Gender differences in treatment outcomes of tuberculosis patients in Taiwan: a prospective observational study

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Abstract

Gender disparities in tuberculosis (TB) cases are reported worldwide, and socio-cultural factors have been proposed as possible causes. To date, gender differences in treatment outcomes of TB patients remain controversial. In this prospective observational study, newly diagnosed, culture-proven TB patients from six hospitals in Taiwan were enrolled for analysis. Gender differences in demographic characteristics and treatment outcomes, including sputum conversion and on-treatment mortality, were analysed accordingly. From January 2007 through to December 2009, a total of 1059 patients were enrolled, including 819 (77.3%) males and 240 (22.7%) females. The ratio of male gender was around 50∼60% in TB patients below 35 years and >80% for those older than 65 years. When compared with the female patients, the male patients were older, more likely to have the habit of smoking, chronic obstructive pulmonary disorder, malignancy and liver cirrhosis, and more likely to present with haemoptysis, body weight loss and pleural effusion. Regarding treatment outcomes, male gender is associated with a lower 2-month sputum culture conversion rate (78.8% vs. 89.3%, p 0.002) and higher on-treatment mortality (21.1% vs. 12.1%, p 0.002). Kaplan–Meier survival analysis demonstrated significantly higher mortality in the men (p 0.005). In multivariate analysis, male gender was an independent risk factor for 2-month sputum culture un-conversion (OR, 1.96; 95% CI, 1.12–3.41). Our findings suggest that male gender is associated with older age, more co-morbidities and worse treatment outcomes. Gender-specific strategies, including active case finding in elderly women and smoking cessation in male patients, are warranted to optimize TB management.

Keywords: Gender, mortality, outcomes, sputum conversion, tuberculosis
Original Submission: 17 January 2012; **Accepted:** 21 May 2012
Editor: M. Drancourt
Article published online: 25 May 2012
Clin Microbiol Infect 2012; **18:** E331–E337
10.1111/j.1469-0691.2012.03931.x

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Introduction

Tuberculosis (TB) is an airborne-transmitted infectious disease with high morbidity and mortality around the world. It is estimated that one-third of the world's total population, nearly two billion people, are infected with TB bacilli and that this caused 1.2–1.5 million deaths in 2010 [1]. Despite a high degree of medical accessibility, abundant medical resources and the implementation of Direct Observation Therapy/Short course (DOTS) programmes since 2006, Taiwan remains a TB endemic area. From 2008 to 2010, the incidence rates of TB in Taiwan were 62.0, 57.8 and 57.2 per 100 000 population, respectively [2]. Our recent studies

reported that the 2-month sputum culture conversion rate was 73.6%, and the 1-year cumulative mortality rate 22.5% in pulmonary tuberculosis patients in Taiwan [3,4].

Gender disparities in TB epidemics are striking and have been well described in previous studies [5–10]. The World Health Organization reported that nearly twice as many men as women have been diagnosed with TB globally [1]. The imbalance in incidence is usually explained by social-cultural-economical factors. The financial dependence and cultural inequality of women result in a lack of autonomy in some areas, which may reduce medical accessibility and treatment adherence [6,8,9]. Gender-specific social roles may also require men to have more social contact, thereby increasing the risk of TB exposure [5,10]. Of note, most of these hypotheses were based on observations from areas with limited medical resources and also with significant socio-cultural differences between genders. Meanwhile, the possible impact of sexual hormones and the differences between men and women in immunological reactions have also been proposed as factors causing men to be more susceptible to *Mycobacterium tuberculosis* infection [11,12].

The impact of gender in treatment outcomes has less frequently been analysed and has revealed inconsistent results. If the socio-cultural characteristics play a role in gender differences in TB epidemics, they may affect the treatment outcomes between genders. Clarifying the gender disparities in treatment outcomes also provides important information for public health strategies against TB disease. The main purpose of the present study was to identify the gender differences of treatment outcomes in TB patients. The clinical and radiographic presentations of TB in male and female patients were also compared.

Methods

Patients and setting

This prospective observational study was conducted at six hospitals in Taiwan, including five tertiary medical centres and one regional hospital that specialized in pulmonary diseases. The involved hospitals were located across all of Taiwan. Newly diagnosed, culture-proven tuberculosis patients from January 2007 to December 2009 were eligible for this study. All patients eligible for recruitment were in- and outpatients and the recruitment was sequential. Patients who were younger than 18 years of age, with treatment default and transferred out were excluded. The demographic profiles (age, gender and co-morbidities) and clinical characteristics (presenting symptoms/signs, smoking habits and history of previous anti-TB treatment) were obtained from the patients and/or their caregivers by enrollment interviews. The findings from radiography of the chest were reviewed by the physicians that were in charge of each hospital and determined at the time of TB diagnosis. The institutional review boards of all six hospitals approved the study and informed consent was obtained from each patient before enrollment.

Treatment of TB

All of the patients were treated with a standard anti-TB treatment that included isoniazid, rifampicin, ethambutol and pyrazinamide in the intensive phase for at least 2 months, followed by a regimen that included isoniazid, rifampicin and ethambutol in the continuous phase. The regimen was modified when the drug susceptibility results were available or when clinically significant adverse effects occurred. We used the adherence to DOTS strategy as a surrogate for treatment compliance. Newly diagnosed TB patients who started the DOTS immediately after TB diagnosis and continued without interruption throughout the treatment course of the initial 2 months were defined as adherence to DOTS strategy.

Treatment outcomes evaluation

In patients with pulmonary involvement, at least two sets of sputum were collected for AFB smears and *Mycobacterium tuberculosis* (MTB) cultures at the end of the second month after initiation of anti-TB treatment. All of the patients were prospectively followed until death or completion of anti-TB treatment. Patients who died for any reason before the completion of anti-TB treatment were included in the analysis. The treatment outcomes evaluated in this study included sputum smear conversion at 2 months, sputum culture conversion at 2 months, mortality at 2 and 6 months and overall on-treatment mortality.

Mycobacteriology and genotyping

Sputum smears were examined through Ziehl–Neelsen staining and MTB cultures were performed in liquid medium (BACTEC MGIT960) and/or Lowenstein-Jensen solid medium. All clinical isolates were genotyped using a commercial spoligotyping kit (Isogen Bioscience B.V., Maarssen, the Netherlands) after genomic DNA extraction [13]. The 'Beijing strain' was defined as a deletion from spacer 1 to spacer 34 in the direct repeat region and the presence of (at least 3) spacers in 35–43.

Statistical analysis

Comparisons of demographic and clinical characteristics were carried out using the chi-squared test or Fisher's exact test for categorical variables, and the two-tailed independent

t-test for continuous variables. The 2- and 6-month sputum conversion status between male and female TB patients was compared by the chi-squared test or Fisher's exact test. The on-treatment mortality was analysed by Cox proportional-hazards models. A p value of <0.1 in the unadjusted model was required for a variable to be entered into the adjusted model. The odds ratios and hazard ratios with their 95% confidence intervals were reported accordingly. In survival time analysis, Kaplan–Meier plots were constructed and log-rank tests were performed. Significance was defined as p <0.05 (two-tailed). Statistical analysis was performed using a statistical software package (SPSS version 14.0; SPSS Inc., Chicago, IL, USA).

Results

From January 2007 to December 2009, 1090 newly diagnosed, culture-proven tuberculosis patients were included from six hospitals. Twenty-three patients were excluded as they were <18 years old, three patients were excluded due to treatment default, and five patients were excluded due to being transferred out. Finally, a total of 1059 patients were enrolled for analysis. Of these patients, 819 (77.3%) were male and 240 (22.7%) were female. The proportions of male gender among various age groups are shown in Fig. 1. The ratio of male gender was around 50~60% for those below 35 years, but escalated gradually as the age of the patients increased. The ratio of male gender was >80% in TB patients older than 65 years.

The demographic characteristics and clinical presentations of the male and female TB patients are shown in Table 1. As compared with the female patients, male TB patients were more likely to be older (66.8 ± 17.8 years vs. 57.4 ± 21.8 years, p <0.001), have the habit of smoking (35.3% vs. 8.3%, p <0.001), have chronic obstructive pulmonary disease (8.8% vs. 1.7%, p <0.001) and have some malignancy (14.9% vs. 7.9%, p 0.005). In Taiwan, most liver cirrhosis is related to viral hepatitis that is induced by the hepatitis B and hepatitis C viruses [14], and we found that men were more likely to have liver cirrhosis (3.9% vs. 1.3%, p 0.043). The drug susceptibility profiles for first line anti-TB drugs and genotypes of MTB isolates were similar between the male and female patients. In clinical presentations, the male TB patients were more likely to present with haemoptysis (17.7% vs. 10%, p 0.004), body weight loss (22.5% vs. 16.3%, p 0.038) and pleural effusion in chest radiograms (22.2% vs. 10.8%, p <0.001) when compared with the female patients. The Beijing genotype was the dominant strain in our patients (479/1059, 45.2%) and the proportions of the Beijing genotype were comparable between male and female patients (46.4% vs. 41.3%, p 0.16).

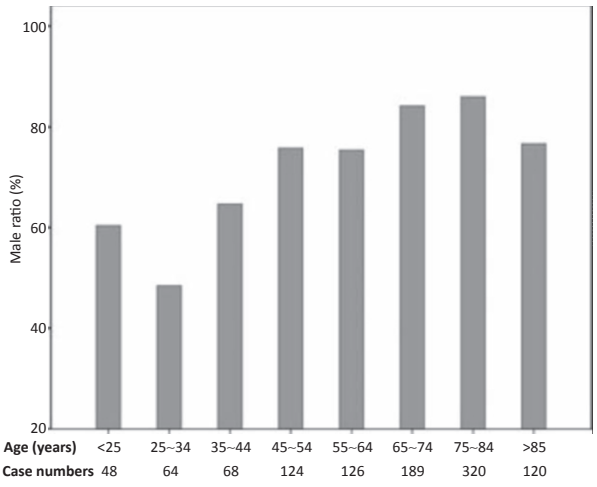

FIG. 1. Male ratios among tuberculosis patients, stratified by age-group.

Comparisons of treatment outcomes between the male and female TB patients are shown in Table 2. Male TB patients were associated with a lower 2-month smear conversion rate (73.6% vs. 84.2%, p 0.004) and a lower 2-month culture conversion rate (78.8% vs. 89.3%, p 0.002). Regarding mortality, male TB patients were associated with higher 6-month mortality (17.2% vs. 10.8%, p 0.017) and higher overall on-treatment mortality (21.1% vs. 12.1%, p 0.002). Kaplan–Meier survival curves according to gender demonstrated higher mortality (p 0.005) in male TB patients (Fig. 2). Multivariate analyses of the clinical predictors for treatment outcomes are shown in Table 3. Male gender, positive pretreatment smear, presence of dyspnoea, presence of cavity and pleural effusion in radiograms and resistance to rifampicin were independent predictors for sputum culture un-conversion at 2 months. Regarding mortality, older age, co-morbidities of malignancy, renal insufficiency, absence of cough for >3 weeks, presence of fever, anorexia, presence of consolidative lesions and pleural effusion in radiograms were independent risk factors associated with higher overall on-treatment mortality.

Discussion

In this prospective observational study, we demonstrated the changing pattern of the male/female ratio among various age groups in Taiwan, a TB endemic area with abundant medical resources and relatively low socioeconomic disparities between men and women. The male patients were older, smoked more frequently, had more co-morbidities and were

TABLE 1. Demographic characteristics and clinical presentations of male and female pulmonary tuberculosis patients[a]

	All patients (*n* = 1059)	Gender		p value
		Male (*n* = 819)	Female (*n* = 240)	
Mean age (SD)	64.7 (19.2)	66.8 (17.8)	57.4 (21.8)	<0.001
Previous TB history	98 (9.3%)	80 (9.8%)	18 (7.5%)	0.29
Smoking habit	309 (29.2%)	289 (35.3%)	20 (8.3%)	<0.001
Initial sputum smear positive	494 (46.6%)	389 (47.5%)	105 (43.8%)	0.31
With extrapulmonary involvement	94 (8.9%)	70 (8.5%)	24 (10.0%)	0.49
Co-morbid diseases				
Diabetes	234 (22.1%)	191 (23.3%)	43 (17.9%)	0.08
COPD	76 (7.2%)	72 (8.8%)	4 (1.7%)	<0.001
Malignancy	141 (13.3%)	122 (14.9%)	19 (7.9%)	0.005
Renal insufficiency	54 (5.1%)	44 (5.4%)	10 (4.2%)	0.46
Liver cirrhosis	35 (3.3%)	32 (3.9%)	3 (1.3%)	0.043
HIV positive	14 (1.3%)	13 (1.6%)	1 (0.4%)	0.21
Post-gastrectomy	33 (3.1%)	29 (3.6%)	4 (1.7%)	0.14
Drug susceptibility test				
Isoniazid resistance	126 (11.9%)	104 (12.7%)	22 (9.2%)	0.14
Rifampicin resistance	68 (6.4%)	55 (6.7%)	13 (5.4%)	0.47
Ethambutol resistance	74 (7.0%)	60 (7.3%)	14 (5.8%)	0.43
Streptomycin resistance	114 (10.8%)	87 (10.6%)	27 (11.3%)	0.78
MDR	62 (5.9%)	49 (6.0%)	13 (5.4%)	0.74
Radiographic presentations				
Cavity formation	187 (17.7%)	146 (17.8%)	41 (17.1%)	0.79
Lobar/segmental consolidation	829 (78.3%)	641 (78.3%)	188 (78.3%)	0.98
Bilateral involvement	423 (39.9%)	339 (41.4%)	84 (35.0%)	0.08
Pleural effusion	208 (19.6%)	182 (22.2%)	26 (10.8%)	<0.001
Presenting symptoms				
Chronic cough	602 (56.8%)	467 (57.0%)	135 (56.3%)	0.83
Haemoptysis	169 (16.0%)	145 (17.7%)	24 (10.0%)	0.004
Dyspnoea	254 (24.0)	199 (24.3%)	55 (22.9%)	0.66
Body weight loss	223 (21.1%)	184 (22.5%)	39 (16.3%)	0.038
Fever	322 (30.4%)	250 (30.5%)	72 (30.0%)	0.88
Malaise	151 (14.3%)	119 (14.5%)	32 (13.3%)	0.64
Anorexia	202 (19.1%)	157 (19.2%)	45 (18.8%)	0.88
Beijing strain infection	479 (45.2%)	380 (46.4%)	99 (41.3%)	0.16
DOTS implementation	520 (49.1%)	396 (48.4%)	124 (51.7%)	0.37

COPD, chronic obstructive pulmonary disorder; HIV, human immunodeficiency virus; MDR, multi-drug resistance; DOTS, directly observed therapy, short course.
[a]Data are presented as mean ± SD or *n* (%), unless otherwise stated.

TABLE 2. Treatment outcomes between male and female tuberculosis patients[a]

	Gender		p value
	Male	Female	
Sputum conversion at 2 months (*n* = 771)			
Smear conversion	437 (73.6%)	149 (84.2%)	0.004
Culture conversion	468 (78.8%)	158 (89.3%)	0.002
Mortality (*n* = 1059)			
At 2 months	90 (11.0%)	18 (7.5%)	0.12
At 6 months	141 (17.2%)	26 (10.8%)	0.017
Overall on-treatment mortality	173 (21.1%)	29 (12.1%)	0.002

Two-month sputum conversion results were available in 771 patients.
[a]Data are presented as mean ± SD or *n* (%), unless otherwise stated.

more symptomatic on initial presentation. Most importantly, we found that the male TB patients had a lower 2-month sputum culture conversion rate and higher on-treatment mortality compared with females. Our findings disclose the differences between male and female TB patients with regards to clinical characteristics and their possible impact on treatment outcomes. Gender-specific strategies are required for better TB control in TB endemic areas.

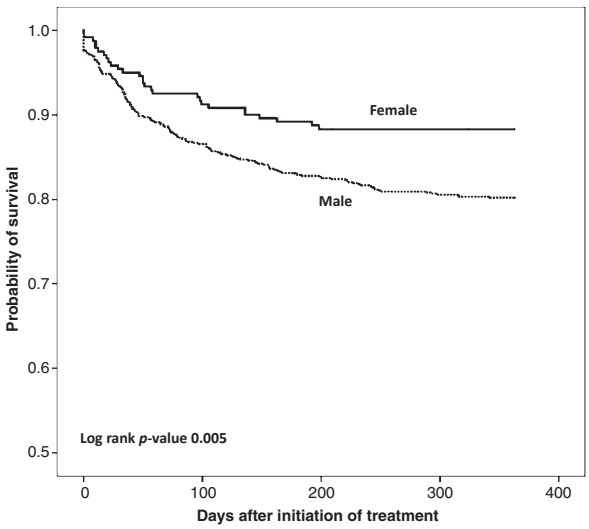

FIG. 2. Kaplan–Meier survival curves of tuberculosis patients stratified by gender. Significance was tested using the log-rank test.

Older age and co-morbidities associated with senility, including diabetes, renal insufficiency and malignancy, are all well-documented risk factors for tuberculosis [15–17]. In the present study, we found that male TB patients were signifi-

TABLE 3. Univariate and multivariate analysis of independent factors associated with 2-month culture conversion and on-treatment mortality in tuberculosis patients[a]

	Two-month culture conversion[a]				Overall on-treatment mortality[b]			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Male gender	2.24 (1.34–3.75)	0.002	1.96 (1.12–3.41)	0.018	1.83 (1.23–2.71)	0.003	–	–
Age	1.00 (0.99–1.01)	0.93	–	–	1.06 (1.04–1.07)	<0.001	1.05 (1.03–1.06)	<0.001
Smoking habit	1.43 (0.99–2.08)	0.06	–	–	0.78 (0.57–1.08)	0.13	–	–
Previous anti-TB treatment	2.49 (1.45–4.28)	0.001	–	–	0.93 (0.57–1.50)	0.76	–	–
Pretreatment smear positive	2.83 (1.91–4.19)	<0.001	2.75 (1.78–4.24)	<0.001	0.92 (0.69–1.21)	0.53	–	–
Diabetes	1.16 (0.76–1.77)	0.50	–	–	1.14 (0.82–1.57)	0.44	–	–
COPD	1.76 (0.97–3.17)	0.06	–	–	1.45 (0.92–2.31)	0.11	–	–
Malignancy	1.21 (0.71–2.06)	0.48	–	–	3.41 (2.53–4.60)	<0.001	2.48 (1.81–3.40)	<0.001
Renal insufficiency	1.00 (0.40–2.47)	0.99	–	–	3.00 (1.94–4.63)	<0.001	2.26 (1.43–3.56)	<0.001
Gastrectomy	1.02 (0.34–3.07)	0.98	–	–	2.69 (1.56–4.62)	<0.001	–	–
Cough >3 weeks	1.40 (0.96–2.06)	0.09	–	–	0.49 (0.37–0.65)	<0.001	0.57 (0.42–0.76)	<0.001
Haemoptysis	1.12 (0.69–1.82)	0.64	–	–	1.15 (0.80–1.66)	0.44	–	–
Dyspnoea	2.03 (1.38–3.00)	<0.001	1.68 (1.10–2.56)	0.017	1.35 (0.99–1.82)	0.05	–	–
Body weight loss	1.28 (0.85–1.93)	0.25	–	–	0.76 (0.53–1.09)	0.13	–	–
Fever	1.36 (0.93–2.00)	0.11	–	–	1.80 (1.37–2.39)	<0.001	1.42 (1.06–1.90)	0.020
Anorexia	1.26 (0.81–1.96)	0.31	–	–	1.58 (1.15–2.16)	0.005	1.43 (1.03–1.98)	0.031
Cavitary lesion	2.76 (1.85–4.11)	<0.001	1.93 (1.24–3.00)	0.004	0.55 (0.35–0.85)	0.007	–	–
Lobar/segmental consolidation	1.00 (0.64–1.55)	0.98	–	–	1.73 (1.16–2.56)	0.007	1.70 (1.14–2.53)	0.009
Pleural effusion	1.94 (1.25–3.01)	0.003	1.76 (1.09–2.86)	0.021	2.50 (1.87–3.33)	<0.001	1.64 (1.20–2.25)	0.002
Resistance to isoniazid	1.60 (0.92–2.79)	0.10	–	–	0.98 (0.64–1.51)	0.94	–	–
Resistance to rifampicin	3.83 (1.96–7.46)	<0.001	3.23 (1.55–6.76)	0.002	0.88 (0.49–1.58)	0.67	–	–
DOTS implementation	0.59 (0.41∼0.85)	0.004	0.57 (0.38–0.86)	0.007	0.90 (0.66–1.23)	0.90	–	–

OR, odds ratio; CI, confidence interval; HR, hazard ratio; COPD, chronic obstructive pulmonary disorder; DOTS, directly observed therapy, short course.
[a]Odds ratios and 95% confidence intervals were derived from the logistic regression analysis.
[b]Hazard ratios and 95% confidence intervals were derived from the Cox proportional hazards model.

cantly older and had more co-morbidities than female patients. We further analysed the male/female ratio of TB patients among various age groups and noted that the proportion of males escalated as age increased. Our findings clearly demonstrate that the gender differences in TB epidemics in Taiwan mostly occurred in elderly patients. In Taiwan, the socio-cultural disparities between genders are not remarkable and medical accessibility is high, as 99% of the population is provided with universal medical coverage by the National Health Insurance Programme. The nearly equal ratio between genders under the age of 45 indicates the even status between middle-aged men and women. However, the dominance of male gender in elderly TB patients is an important issue worthy of study. Higher probabilities of co-morbidities in men may contribute to this male predominance. Neglected socioeconomic barriers may also exist and hinder healthcare-seeking behaviour in elderly females. Under-diagnosis of TB in elderly women is a pivotal issue in TB management and should be carefully evaluated in Taiwan and other developed countries.

The demographic characteristics and clinical presentations of male and female TB patients were also evaluated in this study. Male TB patients were more likely to have the habit of smoking, which has been well documented as a strong risk factor for TB occurrence in several cohort studies [18,19]. The higher smoking rate in men may be an important factor contributing to the higher proportion of men in TB epidemiology. Regarding clinical presentations, women were found to be less symptomatic as compared with male patients. A national tuberculosis survey in Bangladesh described a lower awareness of symptoms among female TB patients [20]. Thorson *et al.* [21] also reported less advanced radiographic findings in women with TB. The absence of respiratory and constitutional symptoms may lead to a delay in seeking medical assistance. Less advanced radiographic findings also make it less likely that physicians will suspect pulmonary TB. Although details about delays in diagnosis were not collected in the present study, all of these factors may contribute to a delayed diagnosis of TB in women.

The impact of gender in treatment outcomes of TB patients has been evaluated in previous studies but has revealed inconsistent results. Higher mortality, greater treatment failure and more default from treatment have been reported in Mexico, India and Italy [22–24]. In contrast, similar treatment outcomes between genders have also been reported in Brazil and Egypt [25,26]. However, gender differences in sputum conversion have rarely been mentioned before. Interestingly, we reported a significantly lower sputum conversion rate and higher on-treatment mortality in male TB patients. In multivariate analysis, male gender was an independent factor associated with failure of 2-month sputum culture conversion.

In our analysis, we found that the presence of cough for >3 weeks was associated with lower mortality. In clinical

practice, the presence of respiratory symptoms, especially chronic cough, is an important indicator that reminds clinicians of the possibility of pulmonary tuberculosis in TB endemic areas. By comparison, pulmonary tuberculosis patients without remarkable respiratory symptoms are probably more likely to have a delayed diagnosis. The delayed diagnosis leads to delayed treatment and worse treatment outcomes. The association between mortality and the absence of cough has also been reported in a previous study [27].

In addition to the aforementioned differences in demographic characteristics, different hormonal effects between genders should also be considered as a possible contributor to inferior outcomes in men. Differences in sexual hormones may lead to inequalities between genders in tuberculosis. Several in-vitro studies evaluated the impact of sex hormones on immune response [28–30]. Generally speaking, oestrogen can enhance the secretion of IFN-γ and potentiate macrophage activation; however, testosterone may inhibit the immune response. In addition, mice studies have demonstrated that ovariectomized mice are vulnerable to *Mycobacterium avium* infection, and that oestradiol supplements may reverse the greater susceptibility [31]. Currently, human studies evaluating the role of sex hormones in TB infection are lacking. However, as there are studies indicating that the immune-modulating effect of sex hormones may potentially contribute to the gender disparity in TB epidemiology, further studies are warranted to elucidate this issue.

Our findings suggest that even in a developed country with abundant medical accessibility such as Taiwan, the gender disparities in tuberculosis remain remarkable. The differences, including demographic characteristics, clinical presentations and treatment outcomes, highlight the importance of gender-specific strategies in TB management. The lower female ratio in the elderly population and fewer symptoms in women raise the concern about delayed diagnosis. The accessibility of medical treatment to elderly women should be re-evaluated, and clinicians should be aware of the lower amount of symptomatic presentations noted among female TB patients. For men, a campaign of smoking cessation should be a pivotal issue to help lower TB occurrence. In addition, early identification and optimal control of the underlying co-morbidities would be helpful in improving the treatment outcomes of TB patients.

There are several limitations to this study. The duration of presenting symptoms at TB diagnosis was not recorded in our patients, and this made it difficult to identify differences in delays between genders. Five of the six study hospitals were referral medical centres, and TB patients with a higher severity or more co-morbidities may have been included, thus causing bias in the evaluation of treatment outcomes. We did not divide deaths as being TB related or non-TB related due to the difficulties in evaluating the impact of TB on mortality. All-cause mortality is more objective and applicable in clinical practice. Finally, the study was performed in a developed country with a low HIV prevalence, and HIV testing was not routinely carried out in each patient. This limited the ability of our findings to be applied to low to middle-income countries or HIV endemic areas.

In conclusion, we found that more than three-fourths of TB patients were male in Taiwan, and that the male/female ratio was higher in the elderly population. Men with TB were older, more likely to be smokers and had more co-morbidities, but women were less symptomatic. Regarding treatment outcomes, female gender was an independent predictor of 2-month sputum culture conversion. The gender disparities in epidemiology and treatment outcomes indicate the importance of gender-specific strategies in TB management. Further studies focusing on immunological characteristics are also warranted to elucidate gender differences other than socio-cultural and clinical factors.

Acknowledgements

This study was funded by the Institute for Biotechnology and Medicine Industry, Taiwan, and the Taipei Veterans General Hospital (V97C1-064, V98C1-039, V98A-086, V99C1-181, V99A-023 and V100A-002).

Transparency Declaration

All authors declare no conflict of interest of any nature.

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